Respiratory Medicine (2007) **101**, 177–185

ELSEVIER

respiratoryMEDICINE

The prevalence of osteoporosis in patients with chronic obstructive pulmonary disease—A cross sectional study

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Received 23 May 2005; accepted 25 March 2006

KEYWORDS
Secondary osteoporosis;
Corticosteroid induced osteoporosis;
COPD;
Vertebral fractures;
Pulmonary function

Summary Chronic obstructive pulmonary disease (COPD) is a complex disease, where the initial symptoms are often cough as a result of excessive mucus production and dyspnea. With disease progression several other symptoms may develop, and patients with moderate to severe COPD have often multiorganic disease with severely impaired respiratory dysfunction, decreased physical activity, right ventricular failure of the heart, and a decreased quality of life. In addition osteoporosis might develop possibly due to a number of factors related to the disease. We wanted to investigate the prevalence of osteoporosis in a population of patients with severe COPD as well as to correlate the use of glucocorticoid treatment to the occurrence of osteoporosis in this population. Outpatients from the respiratory unit with COPD, a history of forced expiratory volume in 1 s (FEV1) less than 1.3 L, with FEV1% pred. ranging from 17.3% to 45.3% (mean 31.4%, standard deviation (SD) 7.3%). Patients between 50 and 70 years were included. Other causes of osteoporosis were excluded before inclusion. At study entry spirometry, X-ray of the spine (to evaluate presence of vertebral fractures), and bone mineral density of lumbar spine and hip were performed. Of 181 patients invited by mail, 62 patients were included (46 females and 16 males). All had symptoms of COPD such as exertional dyspnea, productive cough, limitations in physical activity etc. The mean FEV1 was 0.90 L (SD: 0.43 L) and the mean FEV1% pred. of 32.6% (SD: 14.1%). All had sufficient daily intake of calcium and vitamin D. In 15 patients, X-ray revealed

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0954-6111/$ - see front matter
doi:10.1016/j.rmed.2006.03.029

compression fractures previously not diagnosed. Bone density measurements showed osteoporosis in 22 patients and osteopenia in 16. In total, 26 of the COPD patients were osteoporotic as evaluated from both X-ray and bone density determinations. Thus 68% of the participants had osteoporosis or osteopenia, but glucocorticoid use alone could not explain the increased prevalence of osteoporosis. A large fraction of these needed treatment for severe osteoporosis in order to prevent further bone loss and to reduce future risk of osteoporotic fractures. Thus, there is a significant need to screen patients with COPD to select the individuals in risk of fracture and to initiate prophylaxis or treatment for the disease.

Introduction

Chronic obstructive pulmonary disease (COPD) is a complex disease, where the initial symptoms are often cough as a result of excessive mucus production and dyspnea. With disease progression several other symptoms may develop, and patients with moderate to severe COPD often have multiorganic disease with severely impaired respiratory dysfunction, decreased physical activity, right ventricular failure of the heart, and a decreased quality of life. As the disease progresses, osteoporosis becomes a more prevalent finding in the COPD patient population.[1,2] Osteoporosis is characterized by low bone mass with microarchitectural changes in bone, which leads to an increased susceptibility to fractures. The osteoporosis related fractures are primarily located to the hip, wrist, and the thoracic and lumbar spine. Fractures cause significant morbidity to the patient, such as severe pain, disabilities, decreased mobility, impaired respiratory function, and in worst case, death. Patients with COPD have a multi organic illness initially presenting as cough due to excessive mucus production. These patients often have had immodest tobacco consumption for several years, but also environmental and occupational factors may contribute to the disease most likely as additive to the effects of cigarette smoking. Episodes of mucopurulent relapses increase in incidence and often progresses into chronic obstructive disease. Peripheral oedema as a result of right ventricular failure may develop as well as cyanosis and the patient may experience significant decreases in quality of life due to respiratory dysfunction and inactivity as well as anxiety. Osteoporosis is often disabling in these patients, and may be equally disabling as COPD it self. However, osteoporosis is often undiagnosed in these patients, and may impair respiratory function even further, if the patient experiences vertebral compressions and loss of height.[1,3] Increased awareness is therefore essential in order to diagnose and treat bone loss to reduce the risk of fractures.

Although COPD is a frequent illness with many factors of possible importance for development of several other diseases, only few but excellent reviews on the relationship between COPD and osteoporosis have been published.[3–7] One of the most obvious causes of osteoporosis in these patients is treatment with glucocorticoids, both as systemic therapy and as inhaled glucocorticoids.[8–10] However, the use of glucocorticoids in the treatment of COPD is controversial, but most studies find only a beneficial effect when administered to the most severely affected patients with tendency to exacerbations.[11–13] Glucocorticoid use does not fully account for the low bone mineral density (BMD) and high prevalence of osteoporosis in COPD patients.[3] Even in glucocorticoid naïve patients, BMD is found to be lower than in age-matched control subjects, and consequently, fracture risk higher.[14,15] A number of factors have been suggested to account for these findings. COPD patients are often smokers, as well as they have impaired mobility due to decreased muscle mass and respiratory dysfunction. Further, the group of patients with the most severe COPD also have lower weight than the general population, and low BMI is further a risk factor of increased mortality.[16] In COPD patients, hypogonadism is also more frequent as hypogonadism is commonly occurring in chronic diseases.[3,14] All these factors are known to pre-dispose to osteoporosis, and can explain the increased prevalence.

The present study has aimed at estimating the frequency of osteoporosis in a homogenous population of COPD patients with severe illness. Further, we have evaluated the correlation between the type and dose of corticosteroid intake and the severity of osteoporosis.

Methods

Study population and study design

All patients with a known diagnosis of COPD prior to the present study and whom were followed at the

respiratory outpatient clinic at H:S Bispebjerg Hospital were evaluated ($n = 995$). From this group, patients with severe airflow limitation (FEV1 < 1.3 L which corresponded to FEV1% pred. ranging from 17.3% to 45.3% (mean: 31.4%, SD: 7.3%) were invited by mail during spring 1999 to participate in the present study ($n = 181$). Patients were considered eligible for the study if they met the following inclusion criteria: Alive at the time of inclusion, age between 50 and 70 years; chronic obstructive ventilatory insufficiency (FEV1/FVC < 70%) with no normalisation due to either spontaneous variability or treatment. Patients were excluded on the basis of one or more of the following criteria: Rheumatic diseases or other diseases affecting bone or calcium homeostasis, including secondary hyperparathyroidism; endocrine diseases; asthma or established osteoporosis under treatment with bone-active agents.

Ninety one (50%) of the 181 invited patients did not respond or responded that they were not interested in participating in the study, had died since last follow-up at the out patient clinic, or had moved out of the community. Of the 90 subjects interested in participating, only 62 subjects (68% of the ones interested in participating) were included, as 10 patients answered after the study had finished, 9 patients had established osteoporosis (8 women, 1 man) and were excluded on that basis, 9 were excluded due to other reasons. Thus, 34% of the invited study population was included.

A total of 62 COPD patients with a mean (±SD) age of 63.2 (±5.4) years were eligible for inclusion in the study, of whom 46 were female and 16 male. All patients were treated with a daily dose of 500 mg calcium and 5 μg of vitamin D. Nine patients were in continuous oral glucocorticoids treatment. Two of these were treated with doses corresponding to more than 7.5 mg and the remaining 7 were treated with 2.5–7.5 mg/day. The pulmonary function was registered with a mean absolute FEV1 = 0.90 (±0.43) L and mean absolute FVC = 1.67 (±0.59) L. Percent predicted of normal values for FEV1 was 32.6% (±14.1) (range 9.0–82.4%) and for FVC 43.8 (±12.3) (range 19.5–83.1%). Thus, according to the GOLD guidelines patients were classified as having moderate to severe in the III and IV groups. None of the participants had respiratory insufficiency and were using oxygen at home. Baseline demographic data are shown in Table 1. All patients had normal biochemical evaluations, as patients with changes in calcium metabolic parameters were excluded.

The study was designed as a cross-sectional study, based on historical data on concomitant medication combined with clinical data and a questionnaire obtained at the study visit at the outpatient clinic. The study was approved by the Danish Ethics Committee, and study subjects had signed informed consent before performing any study-related procedures.

Methods

Basic demographic and clinical data were collected during June through September 1999 using a questionnaire concerning: Age, gender, previous bone fractures, present and previous medication,

Table 1 Demographic data for all study participants and for males and females separately.

	Mean (± SD), all participants	Mean (± SD), male participants	Mean (± SD), female participants
Age (years)	63.2 (± 5.4)	62.8 (± 5.8)	63.4 (± 5.3)
Height (cm)	164.2 (± 8.5)	174.1 (± 7.2)	160.8 (± 5.9)
Spirometry			
FEV1 (L)	0.90 (± 0.43)	1.07 (± 0.61)	0.84 (± 0.34)
FVC (L)	1.67 (± 0.59)	2.21 (± 0.82)	1.49 (± 0.35)
FEV1% predicted	32.6 (± 14.1)	35.1 (± 19.3)	31.8 (± 12.1)
FVC % predicted	43.8 (± 12.3)	49.2 (± 17.1)	42.0 (± 9.8)
Bone density			
BMD lumbar spine (g/cm^2)	1.027 (± 0.198)	1.089 (± 0.252)	1.005 (± 0.174)
BMD femoral neck (g/cm^2)	0.833 (± 0.162)	0.888 (± 0.138)	0.814 (± 0.167)
T-score lumbar spine	−1.54 (± 1.27)	−1.25 (± 2.08)	−1.58 (± 1.47)
T-score femoral neck	−1.49 (± 1.63)	−1.51 (± 1.08)	−1.54 (± 1.34)
Smoking habits			
Tobacco pack-years	37.3 (± 12.5)	44.9 (± 10.3)	34.6 (± 12.2)

SD: standard deviation; FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity; BMD: bone mineral density.

tobacco consumption (pack years), daily exercise, daily diet and duration of the respiratory disease.

Bone status was determined by radiology assessments and by measurement of bone mineral parameters. X-rays of the thoracic and lumbar spine in two projections were performed. The X-rays were evaluated based on the international criteria. The evaluating radiologist was blinded to the patient's use of glucocorticoids, actual level of lung function or other factors of possible importance. Bone mineral parameters were performed using a Lunar DFXIQ 5001 densitometer. BMD, bone mineral content (BMC), and area were measured at the lumbar spine (vertebrae L2–L4) and at the femoral neck. All parameters were expressed in standard globally accepted terms: BMD (g/cm^2), BMC (g), and area (cm^2). Standardised T-score analyses were used to compare individual bone density determinations for study subjects to those of a young normal control population of the same gender. This was done to standardize the BMD measurements to peak bone mass, which occurs at 30 years of age. The BMD measured is therefore correlated to the peak bone mass and is expressed as a T-score which is the number of standard deviations below or above peak bone mass for the relevant gender. T-score values between -1.0 and -2.5 are definable for osteopenia and T-scores below -2.5 are definable for osteoporosis[17].

Basic laboratory parameters were analyzed in order to exclude patients with other causes of osteoporosis. The following parameters were determined: B-haemoglobin, B-sedimentation ratio, P-creatinin, P-sodium, P-albumin, P-Ca^{2+}, P-calcium (total), S-25-OH-vitamin D, U-creatinin, U-calcium, P-alkaline phosphatase, S-parathyroid hormone.

Pulmonary function test: Absolute values of FEV_1, FVC, and reversibility were performed on a dry-spirometer of the "bell-spirometer" type with the patient in the seated position. Bricanyl was used as bronchodilator. Three measurements were performed and the best results of the three post-bronchodilator determinations were noted. The discrepancy between the highest and lowest value was less than 5%. Percent predicted of normal values for FEV_1 and FVC were calculated according to formulas from Cherniak, pulmonary function testing[18] as they are suitable for use in caucasians above 18 years of age. Different formulas were used for men and women.

Statistics

All statistical analyses were performed using the SPSS statistical software package, version 11.5 (SPSS Inc., Chicago, IL). All results are presented as mean ± 2 standard deviations ($\pm$SD) in description of the demographic data. In the comparison between different groups, results are presented as mean $\pm$ standard error of the mean (SEM). Analysis of variance (ANOVA) has been used as statistical test to compare means in cases where parametric results are handled. Students *T*-test has been used in cases where two groups of parametric data were compared. Nominal data were compared using the χ^2 test.

T score is a statistical transformation of data that represents a measure of the number of standard deviations from mean peak bone mass of normal individuals of the same gender. Each decrease in BMD of one standard deviation increases the risk of an osteoporotic fracture by 100%. Osteopenia is defined as a T-score between -1.0 and -2.5 standard deviations. Osteoporosis is defined as a T-score $\leqslant -2.5$ standard deviation according to the 1994 WHO criteria, and/or one or more low-energy fractures (hip or spine).

Results

Prevalence of osteoporotic fractures

X-ray examination of the vertebral spine was performed for all 62 study participants. X-rays were analyzed for presence of compression fractures. 15 patients (12 women and 3 men) were found to have one or more previously undiagnosed osteoporotic compression fracture when analysed. This should be seen in contrast to, that only 9 had previously diagnosed fractures prior to the study inclusion. Mean age ($\pm$SEM) was 64.5 ($\pm$1.1) years, compared to 62.8 ($\pm$0.8) years for the non-fracture group. Lung function in FEV1 and FVC for both absolute and % predicted of normal values were compared between the fracture and the non-fracture group and results are shown in Table 2. No significant differences in lung function could be demonstrated between the two groups (Table 2 and Fig. 1a). We also tested for differences in smoking habits, but no differences between the fracture and non-fracture groups in tobacco pack-years could be detected. However, as expected a significant difference in BMD at the lumbar spine was detected between the fracture and non-fracture group, showing a higher bone mass in the non-fracture group. Further, a higher percentage of patients in glucocorticoid treatment was found in the fracture group (36.4%) compared to the non-fracture group (11.6%) (Table 2),

Table 2 Comparison of age, lung function tests, bone density parameters, and number of patients with continuous glucocorticoid treatment between the group of patients with newly diagnosed vertebral fractures and the non-fracture group.

	Fracture group $n = 15$, mean ($\pm$SEM)	Non-fracture group $n = 37$, mean ($\pm$SEM)	*P*-value
Age (years) ($n = 62$)	64.5 ($\pm$1.1)	62.8 ($\pm$0.8)	0.29
Spirometry ($n = 56$)			
FEV1 (L)	0.87 ($\pm$0.17)	0.91 ($\pm$0.05)	0.82
FVC (L)	1.64 ($\pm$0.21)	1.68 ($\pm$0.08)	0.83
FEV1% predicted	31.6 ($\pm$5.6)	32.9 ($\pm$1.7)	0.77
FVC % predicted	43.1 ($\pm$4.7)	44.0 ($\pm$1.6)	0.81
Bone density ($n = 54$)			
BMD lumbar spine (g/cm^2)	0.895 ($\pm$0.043)	1.060 ($\pm$0.030)	0.01
BMD femoral neck (g/cm^2)	0.751 ($\pm$0.048	0.854 ($\pm$0.024)	0.06
T-score lumbar spine	$-$2.64 ($\pm$0.35)	$-$1.20 ($\pm$0.25)	$<$0.01
T-score femoral neck	$-$2.17 ($\pm$0.41)	$-$1.37 ($\pm$0.18)	0.06
Smoking habits ($n = 61$)			
Tobacco pack-years	38.2 ($\pm$2.4)	37.0 ($\pm$2.0)	0.76
% glucocorticoid treated ($n = 54$)	36.4%	11.6%	0.07

n: number of individuals; FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity; BMD: bone mineral density; SEM: standard error of the mean.

suggesting a detrimental effect of glucocorticoids on bone strength.

Bone mineral density

Of the 62 patients included, 54 had DXA scans of the hip and lumbar spine performed. Subjects were grouped according to the WHO criteria, and diagnosed as osteoporotic, osteopenic, or normal bone mass according to T-score for BMD. The lowest T-score at either region determined the diagnosis. Thus, if the T-score at either region was below -2.5, the individual was diagnosed as having osteoporosis. If the lowest T-score at either region was between -2.5 and -1.0 the subject was diagnosed with osteopenia. If both hip and lumbar spine T-score was above -1.0 the study subject was grouped as having normal bone mass. Of 54 evaluable patients, 22 patients were diagnosed as having osteoporosis by BMD alone. Sixteen were osteopenic and 16 had normal bone mass. The three disease groups did not differ in age, nor did they show statistically significant differences with respect to absolute or % predicted of normal values of FEV1, FVC or tobacco pack-years (Table 3 and Fig. 1b).

Of the patients diagnosed with osteoporosis according to BMD measurements, 4 had continuous glucocorticoid treatment, while only one in the osteopenic group and 3 in the group with normal bone mass were continuously treated with glucocorticoids. This distribution was not found significant by statistical testing. Finally, the number and percentage of vertebral fractures in three BMD groups were determined. In the group with normal BMD, only 1 patient had a fracture, while 3 in the osteopenic group and 7 in the osteoporotic group had one or more vertebral fractures. However, this result was not found to be significant upon statistical testing.

Prevalence of osteoporosis in a group of COPD patients

The diagnosis of osteoporosis is based both of bone mass measurements and the knowledge of previous low-energy fractures in the individual patient. In this study, we obtained information of both vertebral fractures and bone mass. Combining these data, we found that out of 58 evaluable patients, 26 patients (44.8%) were osteoporotic, while 13 (22.4%) were osteopenic and 15 (25.9%) had normal bone mass. Of the patients diagnosed with osteoporosis 5 had continuous glucocorticoid treatment, while one in the osteopenic group and 3 in the group with normal bone mass. No statistically significant differences could be detected between the three groups with respect to glucocorticoid use (Table 4). We also tested for differences in smoking habits, but no differences between the osteoporotic and non-osteoporotic groups in tobacco pack-years could be detected.

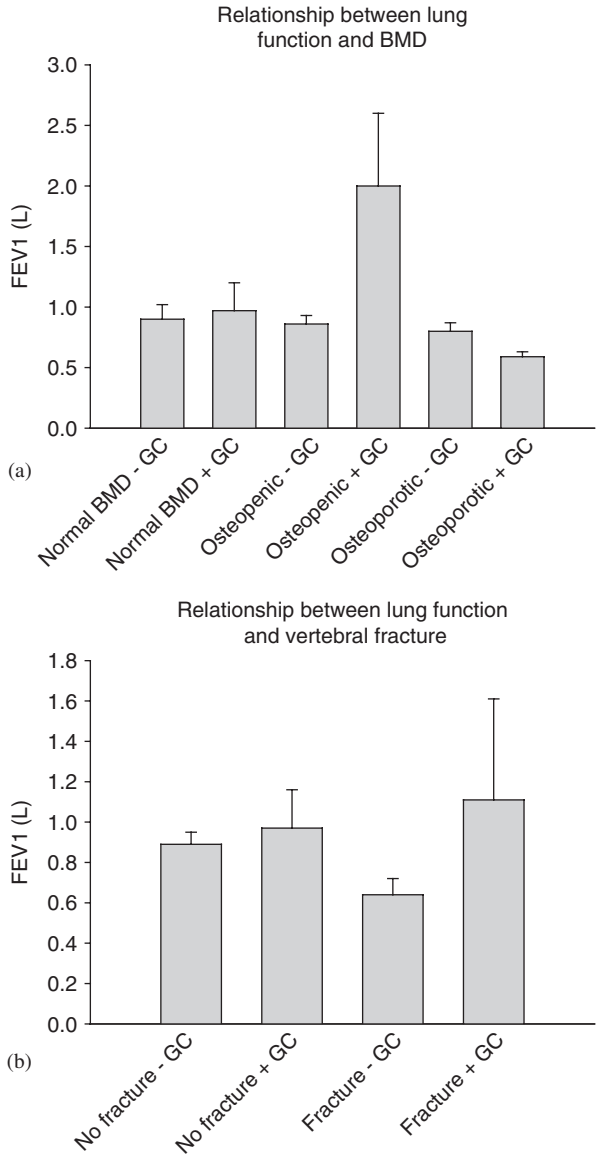

Figure 1 Shows the relationship between lung function and the presence of one or more vertebral fractures in the COPD patients in the study. Average forced expiratory volume in 1 s (FEV1) is shown for four different groups: patients without vertebral fractures not receiving continuous glucocorticoid treatment (''no fracture—GC''), patients without vertebral fractures treated with continuous glucocorticoids (''no fracture+GC''), patients with one or more vertebral fractures not receiving glucocorticoids (''fracture—GC), and finally patients with fracture treated with continuous glucocorticoids (''fracture+GC). Error bars show standard error of the mean. BMD: bone mineral density; FEV1: forced expiratory volume in 1 s; GC: glucocorticoid.

Discussion

The present study shows a high prevalence of osteoporosis among patients with severe COPD (GOLD IIb and III). The group of patients studied is likely to represent the large number of COPD patients followed in the pulmonary out-patient clinics throughout the world. Most countries have guidelines concerning long-term corticosteroid treatment and prevention of secondary osteoporosis, but no countries have guidelines concerning osteoporosis in COPD patients with or without glucocorticoid treatment (oral and inhaled). In the recent years, COPD rehabilitation programs have been part of daily routine, including dietician, activity and smoking cessation and furthermore, use of steroids are recommended due to GOLD classification to be restricted to patients with numerous exacerbations per year. In line with other studies, we show that although glucocorticoid treatment is a major risk factor for osteoporosis in chronically treated COPD patients, other risk factors independent of corticosteroids, but related to the disease, exist. This is evident, as we did not find any difference in prevalence of glucocorticoid treatment in the osteoporotic group versus the group having normal bone mass. A reason for these findings might be that data concerning intake of steroids are retrospectively collected. These risk factors may assume greater significance when the total dose of steroids is low, as in the case of inhalation steroids.[19] Further, in this study, we do not have information regarding the length of corticosteroid treatment, as no valid information regarding length of treatment was available, and thus the number of years patients have been exposed to this medication could not be determined. Thus, in order to determine the exact contribution of glucocorticoids to osteoporosis and fractures in COPD patients prospective studies with collection of data for glucocorticoid dose and length of treatment are necessary. Furthermore, the sample size in this study may also influence the results. The power and the number of patients in glucocorticoid treatment surely invalidates the statistical determination of the influence of risk factors on osteoporosis development.

However, COPD patients have several other risk factors that might contribute to development of osteoporosis such as smoking and inactivity, and these factors might be as important as glucocorticoids as risk factors in these patients. Smoking habits are clearly a risk factor for both osteoporosis and COPD, and could potentially interfere with our results. In the current study we collected information on the patients' number of pack-years, but we could not detect any differences in smoking habits between osteoporotic patients and non-osteoporotic patients. This does not indicate that smoking is not a risk factor of osteoporosis, but it might

Table 3 Comparison of age, lung function tests, glucocorticoid (GC) treatment, and incidence of vertebral fractures between osteoporotic and osteopenic COPD patients, and COPD patients with normal bone mass.

	Normal BMD ($n = 16$), mean ($\pm$SEM)	Osteopenic BMD ($n = 16$), mean ($\pm$SEM)	Osteoporotic BMD ($n = 22$), mean ($\pm$SEM))	*P*-value
Age (years) ($n = 54$)	62.4 ($\pm$1.5)	64.2 ($\pm$1.1)	63.3 ($\pm$1.3)	0.83
Spirometry ($n = 50$)				
FEV1	0.91 ($\pm$0.10)	1.03 ($\pm$0.15)	0.76 ($\pm$0.07)	0.26
FVC	1.62 ($\pm$0.14)	1.82 ($\pm$0.20)	1.58 ($\pm$0.12)	0.65
FEV1% predicted	33.2 ($\pm$3.0)	36.7 ($\pm$4.4)	28.0 ($\pm$2.4)	0.24
FVC % predicted	43.3 ($\pm$2.4)	46.3 ($\pm$3.7)	41.7 ($\pm$2.7)	0.68
Smoking habits ($n = 61$)				
Tobacco pack-years	35.3 ($\pm$4.0)	38.0 ($\pm$3.4)	37.6 ($\pm$2.0)	0.89
No. of continuously GC treated ($n = 54$)	3 (18.8%)	2 (12.5%)	4 (18.2%)	0.87
No. with vertebral fracture ($n = 54$)	1 (6.3%)	3 (18.8%)	7 (31.8%)	0.15

n: number of individuals; FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity; BMD: bone mineral density; SEM: standard error of the mean.

Table 4 Comparison of lung function tests and number of continuously glucocorticoid (GC) treated COPD patients in the osteoporotic group, as determined by a bone mineral density (BMD) T-score at either site of measurement < -2.5 and/or presence of a vertebral fracture on X-ray of the vertebral spine versus the non-osteoporotic group, as determined by a BMD T-score at both spine and hip of > -2.5 and no vertebral fractures on X-ray.

	Osteoporotic group $n = 26$, mean ($\pm$SEM)	Non-osteoporotic group $n = 28$, mean ($\pm$SEM)	*P*-value
Age (years) ($n = 62$)	63.6 ($\pm$1.0)	62.9 ($\pm$1.0)	0.63
Spirometry ($n = 56$)			
FEV1 (L)	0.86 ($\pm$0.09)	0.93 ($\pm$0.07)	0.56
FVC (L)	1.69 ($\pm$0.13)	1.65 ($\pm$0.10)	0.83
FEV1% predicted	31.4 ($\pm$3.2)	33.8 ($\pm$2.1)	0.54
FVC % predicted	44.2 ($\pm$2.9)	43.4 ($\pm$1.7)	0.80
Smoking habits ($n = 61$)			
Tobacco pack-years	37.3 ($\pm$1.6)	37.3 ($\pm$2.7)	0.98
No. of continuously GC treated ($n = 54$)	19.2%	14.3%	0.63

FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity; SEM: standard error of the mean.

suggest that some people do not respond to smoking with decreased bone mass. However, in addition to a genetic component, osteoporosis is strongly affected by environmental factors, and these patients are probably exposed to a number of other factors that might outweigh the effects of smoking on the bones.

Previous papers indicate the need of primary osteoporosis prophylaxis and the estimation of BMD when glucocorticoid treatment is initiated,[20,21] but only few articles focus on secondary osteoporosis relating to inhaled steroid treatment.[22,23] In contrast to these studies, other long-term surveys have failed to demonstrate any detrimental effect of inhaled steroids on bone mass.[24,25]

Our results show reduced BMD (osteopenia or osteoporosis) in approximately 75% of the study group, where a large number of these would be eligible for anti-osteoporotic therapy according to the treatment guidelines in Denmark, as the present group of COPD patients were classified as moderate to severe COPD (GOLD III and IV). None of the patients suffered from any symptoms related to fracture of the vertebrae. Thus, a large number of patients have established osteoporosis, though they do not receive any treatment. They might have

back pain or other symptoms, but the diagnosis of osteoporosis is not given to these patients, thus withholding proper and necessary treatment to prevent further fractures and disability of the patient.

Another reason for the high prevalence of osteoporosis in COPD patients is most likely that there among these patients is a predominance of women. In our study, we see a predominance of women. The incidence of osteoporosis is higher in women than in men, and it could be expected that women with COPD therefore would be even more susceptible to develop osteoporosis than women with normal lung function. It is well-established that women are more prone to develop COPD even if they on an average basis do not smoke as much as men. This is partially because they are less resistant to the harmful side effects of smoking than men, but also that women live longer, and live to an older age with their lung disease.[26]

At study start almost 50% of the initial contacted group did not respond. A number of these were expected to have died, and may thus have had the most severe COPD. Another reason for the patients not to respond could be that they were immobilized and could thus not answer the invitation. Some of the patients were also suspected to have respiratory insufficiency being treated with oxygen at home, and were therefore not able to leave the home. As they non-responders thus are suspected to have the most severe COPD, we would therefore expect these to have an even higher prevalence of osteoporosis. The patients included in this study would therefore be the least ill patients, so the prevalence of bone disease in this study could very well be underestimated, meaning that the problem in the most severely affected COPD population is even bigger than documented. However, we do not have any direct data documenting the respiratory status of the non-responders other than they have moderate to severely decreased lung function. This may bias the results of the study and it could be questioned whether the low participation rate makes it possible to generalize the results of this study to all COPD patients followed in out-patient clinics worldwide. Naturally, the data are only representative of the included population, but as mentioned above there is no reason to think, that the non-responders will have less significant osteoporosis than the included patients.

As expected, no statistically significant differences in the pulmonary function were detected between osteoporotic, osteopenic, and normal individuals. FEV1 was lower compared to the inclusion criteria (FEV1 $\leqslant$ 1.3 L), which is as expected. The group with osteoporotic fractures were recruited to the study as non-osteoporotic COPD patients, as they had no known history of osteoporosis, but as the results show, they are troubled with very low pulmonary function and osteoporosis. The previously unknown fractures may cause back pain and as a result of pain, limitation of the thoracic movements. This may cause pneumonia and further decreased pulmonary function and even lead to further steroid treatment and inactivity. Thus, osteoporotic vertebral fractures in COPD patients lead to a vicious cycle, where if the problem is not recognized and treated, the patients' pulmonary function will decline rapidly.

Surprisingly, we were unable to detect a significant difference in the number of fractures when comparing the three BMD groups (normal, osteopenic, and osteoporotic). This is presumably due to low power of the study with respect to this parameter, as we only see one individual with a vertebral fracture in the normal group. However, when we look at the percentage of individuals with fractures in the three BMD groups, a clear tendency towards increased fracture risk is apparent as the percentage of individuals with fracture increases from 6.3% in the group with normal BMD, 18.8% in the osteopenic group to 31.8% in the osteoporotic group. Thus, a larger number of individuals should be included in order to detect significant differences in fracture risk. Another limitation of the study is that no age- and gender-matched control group has been included. For the determination of BMC we have correlated the measurements of BMD to the values at peak bone mass for a young normal control population in order to standardize the measurements. Values were expressed as T-scores. This was further done as T-scores are actually definable for osteoporosis and osteopenia. However, this does not give information on which osteoporosis prevalence to expect in the patient population. In this study we have only used historical controls, but the use of an age- and gender matched control group in combination with a larger sample size/power would have strengthened the study. However, it could be discussed which population should be used as a control group. It is evident that they should be healthy and be age- and gender matched to the patients included in the study, but as there are many risk factors for osteoporosis in COPD patients, the outcome and the validity of the conclusions would definitely depend on whether the controls are smokers/non-smokers, have low/normal body weight, etc.

Despite the limitations of this study there is no doubt that osteoporosis is a major problem in COPD patients, and patients with severe COPD should have performed diagnostic X-ray/DXA in order to

diagnose osteoporosis[4]. In case of vertebral fractures or DXA verified osteoporosis, anti-osteoporotic treatment should be initiated [7]. This serves two purposes: to reduce future risk of new vertebral fractures, and to slow the onset of terminal COPD, which can be the cause of evolving osteoporosis. Osteopenic patients should be followed closely in order to start anti-osteoporotic treatment as soon as necessary before vertebral fractures occur. Further, if the patient is continuously treated with glucocorticoids, treatment should be initiated already in osteopenic patients according to local recommendations.

In conclusion, the present study showed that there is a high prevalence of accelerated bone loss in the COPD patient population, and that it is important to screen these patients for osteoporosis in order to initiate treatment for the disorder before they develop fractures. Further studies are needed to determine whether this is also true for COPD patients with less severe respiratory disease, and subsequently determining the need for prevention of bone loss in this population.

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